memo

to: Medical Department/Central Files
cc.: Dr. P. Goldenheim
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from: John Savarese, M.D.

dept: Medical

subject: Final Clinical Summary Packages: "Dosing-Range Study Of Controlled-Release Oral Morphine (MS Contin) In Chronic Cancer" -- Study No. 84-0805

date: 7/29/85

Attached please find the above referenced Final Clinical Summary Packages (consisting of Final Clinical Summary, Statistical Report, investigator's curriculum vitae and copy of employed protocol) for the below listed investigators:

1) Dr. R. Houde (Memorial Sloan-Kettering Cancer Center)

and

2) Dr. R. Blum (New York University Medical Center)

John J. Savarese, M.D.
Associate Medical Director

/tn
Encs.

Trial Exhibit
Purdue et al. v. Endo et al.
Nos. 00 Civ. 8029 (SHS); 01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)
DX 3286

2/26/02 GLB

Deposition Exhibit
Purdue et al. v. Endo et al.
Nos. 00 Civ. 8029 (SHS); 01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)
DX 291

01

PURDUE FREDERICK COMPANY

FINAL CLINICAL SUMMARY

DISTRIBUTION:

Protocol No. 84-0805
Product Name: MS Contin
Investigator: Dr. R. Houde
Address: Memorial Sloan-Kettering Cancer Center
City: New York
State: New York

TITLE: DOSING-RANGE STUDY OF CONTROLLED-RELEASE ORAL MORPHINE (MS CONTIN®) IN CHRONIC CANCER

OBJECTIVES

The purpose of this study was to confirm the European experience that MS Contin 30 mg Tablets are safe and effective for the prolonged relief of severe pain when given as a q 12 hour regimen. The study was designed to evaluate MS Contin in a realistic clinical setting via a dosing-range protocol having statistical sensitivity. A spectrum of maintenance doses of MS Contin 30 mg Tablets was determined for cancer patients requiring narcotic analgesia.

MANAGEMENT SUMMARY

Thirty (30) of thirty-eight (38) cancer patients completed this dosing-range study with no dropout attributable to MS Contin. The study was designed to reflect a real clinical situation in which an analgesic is titrated to a level achieving adequate analgesia with acceptable side effects. Patients had previously been prescribed a narcotic analgesic and, overall, these encompassed many of the commonly used narcotics. Regardless of the particular opioid previously used, each patient was successfully converted to MS Contin q 12 h to q 8 h. It was found that these patients could go from an immediate-release morphine sulfate preparation dosed q 4 hours to a MS Contin regimen dosed q 12 h to q 8 h with the majority of patients dosed q 12 h successfully maintained on this regimen. Both patients and Investigator found MS Contin to be equal or better regarding pain control and side effects than immediate-release morphine and prestudy analgesic.

PREPARED BY Jr J. Navarro MD PhD DATE 7/26/85

APPROVED BY Paul S. Goldenheim, MD DATE 7/26/85

INVESTIGATOR Dr. R. Houde DATE _____

CLINICAL SUMMARY

DOSING-RANGE OF CONTROLLED-RELEASE ORAL MORPHINE (MS CONTIN®) IN CHRONIC CANCER-

PROTOCOL NO. 84-0805

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CLINICAL SUMMARY

DOSING-RANGE OF CONTROLLED-RELEASE ORAL MORPHINE (MS CONTIN®) IN CHRONIC CANCER

PROTOCOL NO. 84-0805

ABSTRACT

Thirty (30) of thirty-eight (38) cancer patients completed this dosing-range study with no dropouts attributable to MS Contin. The study was designed to reflect a real clinical situation in which an analgesic is titrated to a level achieving adequate analgesia with acceptable side effcts. Patients had previously been prescribed a narcotic analgesic and, overall, these encompassed many of the commonly used narcotics. Regardless of the particular opioid previously used, each patient was successfully converted to MS Contin q 12 h or q 8 h. It was found that these patients could go from an immediate-release morphine sulfate preparation dosed q 4 h to a MS Contin regimen dosed q 12 h or q 8 h with the majority of patients maintained on a q 12 h regimen.

Both patients and Investigator found MS Contin to be equal or better regarding pain control and side effects than immediate-release morphine and prestudy analgesic. These findings based on a realistic therapeutic study design support the safety and efficacy of MS Contin 30 mg Tablet for the prolonged relief of severe pain when dosed q 12 h with proper dosage adjustment to this twice daily regimen.

CLINICAL SUMMARY

DOSING-RANGE OF CONTROLLED-RELEASE ORAL MORPHINE (MS CONTIN®) IN CHRONIC CANCER

PROTOCOL NO. 84-0805

I INTRODUCTION

It is generally accepted that routinely scheduled analgesic dosing is the preferred treatment of chronic pain in patients with cancer.[1-4] However, despite the wide array of narcotic analgesics previously available for general use no one product approached that of the ideal analgesic. Ideally, an analgesic preparation, used for the treatment of chronic pain, should meet the following criteria:

A. Be orally effective

B. Permit a dosing regimen that is convenient to the patient

C. Prevent breakthrough pain

D. Produce prolonged effective drug levels

E. Be devoid of accumulation properties

Methadone might be considered as a drug that approaches that of the ideal narcotic analgesic for chronic pain management. Unfortunately, methadone, because of its long half-life (24-57 hours) and accumulation potential is not without its difficulties.[5]

MST Continus Tablets, a controlled-release morphine sulfate tablet widely used in Europe, have proven to be an ideal narcotic analgesic for the treatment of chronic severe pain. In European studies MST Continus Tablets have been shown to be orally effective, convenient to use (i.e., can be dosed every 12 hours), prevent breakthrough pain (i.e., analgesia can last 12 hours), produce steady morphine plasma concentrations, and do not accumulate with continued dosing.[6-11] The American formulation called MS Contin 30 mg Tablets (MSC) is equivalent to MST Continus 30 mg Tablet and is now available as a prescription medication.

II OBJECTIVE

The objective of this study was to obtain estimates of the efficacy and side effects of a controlled-release formulation of oral morphine (MSC) relative to immediate-release oral morphine (MSIR) following repeated administrations in cancer patients with chronic pain. The clinical acceptability of MSC dosed q 12 hours or q 8 hours was determined and compared with the analgesia/side effects of the patients' previous narcotic and MSIR dose q 4 h.

III MATERIALS AND METHODS

A. Subjects

Participants in this study were cancer patients of either sex above the age of 18 years who were deemed candidates for narcotic analgesics for control of their pain. Eligibility criteria were structured so as not to exclude the wide range of cancer pain syndromes existent in this patient population. However, patients had to exhibit the characteristics of being compliant, rational, reasonably responsive and capable of subjective evaluation. Such patients had to express a willingness to follow protocol requirements as evidenced by written informed consent. Excluded were patients who had manifested hypersensitivity to morphine. Those who had major organ dysfunction which might adversely affect safety or obscure efficacy were excluded from the study. Reclusive living circumstances were also an exclusion criterion for safety reasons.

B. Medications

1. Test

MS Contin 30 mg Tablets, Lot Nos. CB11-35, CB11-44, 6JS. [MSC]

2. Reference

Morphine Sulfate 15 mg Tablets, Roxane, Lot Nos. 830634, 840759. [MSIR]

Morphine Sulfate 30 mg Tablets, Roxane, Lot Nos. 840792, 840342. [MSIR]

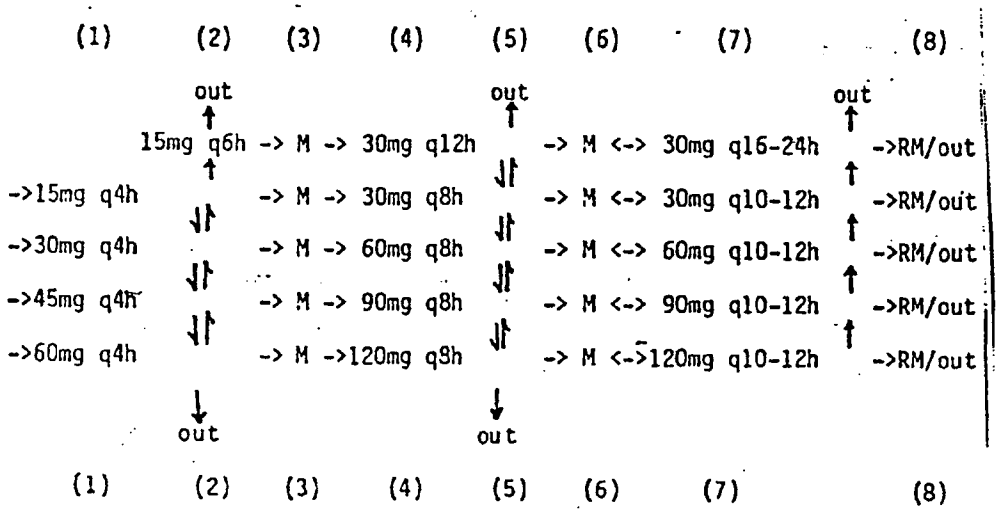
C. Trial Phase

1. Design and Duration

This was a controlled, crossover (sequential), open-label, dosing-range study lasting from approximately one to four weeks at the discretion of the Investigator.

2. Procedure

The following flow-chart diagrams the phases of this study: 1) substitution with MSIR, 2) titration with MSIR, 3) maintenance with MSIR, 4) substitution with MSC, 5) titration with MSC, 6) maintenance (M) with MSC, 7) interval extension titration, 8) routine management (RM) with MSC or out of study.



a. Substitution with MSIR: Phase (1)

IR was substituted for the patient's previous analgesic in an equianalgesic amount of pain reliever in combination with the Analgesic Study Nurse's and/or Physician's judgment as to appropriate therapeutic dose and schedule. More specifically, the previous 48 hour amount of analgesic was mathematically converted to intramuscular morphine sulfate milligram equivalents and divided by 3 using the analgesic equivalency ratios as detailed on the following page. The resulting number assumes an equivalency of 33 mg oral morphine and 10 mg intramuscular morphine and is based on duration of analgesia in contrast to area under the time-effect curves for intramuscular and oral morphine. The resulting number was rounded to the nearest MSIR substitution dose and initally administered q 4 h.

RELATIVE POTENCIES OF ANALGESICS COMMONLY EMPLOYED FOR SEVERE PAIN EXPRESSED IN TERMS OF THE INTRAMUSCULAR (IM) AND ORAL (PO) DOSES APPROXIMATELY EQUIVALENT IN TOTAL EFFECT TO A 10 mg IM DOSE OF MORPHINE

	IM (mg)	PO (mg)	Major Differences from Morphine
OXYMORPHONE (Numorphan)	1	6	None
HYDROMORPHONE (Dilaudid)	1.5	7.5	Shorter acting.
LEVORPHANOL (Levodromoran)	2	4	Relatively high PO to IM potency.
PHENAZOCINE (Prinadol)	3	15	None
METOPON	3	18	None
HEROIN	4		Shorter acting.
DEXTROMORAMIDE (Palfium)	7.5	10	High PO to IM potency.
PIMINODINE (Alvodine)	7.5		None
METHADONE (Dolophine)	10	20	Relatively high PO to IM potency.
MORPHINE	10	60	
OXYCODONE	15	30	Shorter acting. Relatively high PO to IM potency.
DIPIPANONE (Pipadone)	20		None
METHOTRIMEPRAZINE (Levoromo, Nozinan)	20		Phenothiazine - unlike morphine
ANILERIDINE (Leritine)	30	50	Relatively high PO to IM potency.
ALPHAPRODINE (Nisenil)	45		Very short acting.
PENTAZOCINE (Talwin)	60	180	Narcotic antagonist analgesic
MEPERIDINE (Pethidine, Demerol)	75	300	None
CODEINE	130	200	Relatively high PO to IM potency. Relatively more toxic in higher doses.
DEXTROPROXYPHENE (Darvon)	240		Similar to codeine but more toxic in high doses.

RELATIVE POTENCIES OF ANALGESICS EMPLOYED ORALLY FOR LESS SEVERE PAIN EXPRESSED IN TERMS OF DOSES APPROXIMATELY EQUIVALENT IN TOTAL EFFECT TO 650 mg OF ASPIRIN

	PO (mg)	Salient Features
PENTAZOCINE (Talwin)	30	Weak narcotic - narcotic antagonist, high analgesic potential,* low addiction liability.
CODEINE	32	Weak narcotic, high analgesic potential, relatively low addiction liability.
MEPERIDINE (Demerol)	50	Narcotic, high analgesic potential, high addiction liability.
PROPOXYPHENE (Darvon)	65	Weak narcotic, low analgesic potential, low addiction liability.
AMINOPYRINE (Pyramicon)	600	Non-narcotic, low analgesic potential, no addiction liability, risk of agranulocytosis.
ASPIRIN (ASA)	650	Non-narcotic, antiinflammatory, low analgesic potential, no addiction liability or tolerance.
PHENACETIN (Acetophenetidin)	650	Similar to aspirin but with limited antiinflammatory properties.
ACETAMINOPHEN (Paracetamol)	650	Similar to phenacetin, less potential renal toxicity.
SODIUM SALICYLATE	1000	Similar to aspirin.

* "Analgesic potential" refers to level of analgesia attainable by increasing dose to point of limiting side-effects.

b. Titration With MSIR: Phase (2)

Titration with MSIR was primarily in terms of dosage, as opposed to dosing interval, except at the extremes of the permissible dose range and in cases in which the responsible clinicians judged that a change in dosing interval was therapeutically indicated. Acceptable analgesia without unacceptable side effects for up to two consecutive dosage intervals was the indication for decreasing dosage or increasing the dosing interval. In each of the titration phases of this study, patients could have been "titrated

*NOTE: This table has been prepared by the Analgesic Study Section, Memorial Sloan-Kettering Cancer Center.

out". In addition, as in any phase of this study, patients might have been "dropped out" due to unacceptable side effects, and patients could withdraw for any reason.

While criteria for "unacceptable" will differ from patient to patient, an attempt was made to keep these criteria consistent within particular patients throughout the course of the study. Nevertheless, analgesia was generally considered "unacceptable" if the patient requested medication prior to the next scheduled time of medication or if moderate to severe pain at the time of medication was not decreased within two (2) hours following medication.

Titration with MSIR was carried out for as long as necessary to achieve an appropriate dose.

c. Maintenance With MSIR: Phase (3)

Two (2) days of treatment with MSIR without altering dosage or dosing interval was the minimum duration of maintenance with MSIR.

d. Substitution With MSC: Phase (4)

MSC was substituted for MSIR at twice the dosage and half the dosing frequency at up to one (1) hour prior to the next regularly scheduled medication time.

e. Titration With MSC: Phase (5)

Titration with MSC was conducted according to the same criteria as titration with MSIR (Phase 2).

f. Maintenance With MSC: Phase (6)

Two (2) days of treatment with MSC, without the necessity of altering dosage or dosing interval was the minimum duration of maintenance with MSC, as it was for MSIR.

Completion of the protocol through this Phase 6 was considered to constitute a "completed patient."

g. MSC Interval Extension Titration: Phase (7)

The dosing interval was extended, usually in one (1) to two (2) hour increments, in an attempt to determine the longest dosing interval, usually up to 12 hours, which provided acceptable analgesia with repeated administrations of MSC. Comparable criteria for titration decisions were used as in Phases 2 and 5.

The extent and duration of this titration phase was at the discretion of the investigators on an individual patient basis.

3. Evaluations

Usual demography, medical background and prior analgesic history were recorded. Clinical laboratory data previously obtained were reported only if not within normal limits.

a. For Efficacy

i Daily diary of activity, pain intensity, pain relief and side effects were kept by the patients during both the MSIR and MSC phase of the study.

ii A record was kept of the amounts and dosing frequency of test drugs used in the study as well as the quantity of rescue analgesics required.

iii Telephone or in person interviews were done frequently (usually daily) to assess both safety and efficacy.

vi Global evaluation of activity, pain intensity, pain relief and side effects were made by both patient and Nurse-Observer.

v Investigator's Summary of Study.

b. For Safety

Adverse experiences (serious and unexpected untoward reactions), whether spontaneously reported or elicited upon direct questioning, were recorded and evaluated promptly by the Investigator to determine the severity, duration, initiation of corrective measures, if warranted, and subjects followed until "normal".

IV RESULTS

A. Background

Thirty-eight (38) cancer patients were entered and thirty (30) completed the study. Demographic information is given in Table 1. The eight dropout patients were discontinued for a variety of reasons none related specifically or solely to MS Contin as described in Table 2. The patients' prestudy analgesic regimens are displayed in Table 3.

B. Efficacy Evaluations

All patients completing the study were controlled on MSIR dosed at a q 4 hour regimen and successfully switched to MSC dosed q 12 h or q 8 h. Table 4 indicates that nearly half of the patients were controlled on the q 12 h regimen. However, 100% of patients who were tried on the twice daily program did achieve acceptable analgesia with acceptable side effects. The total daily amount of morphine given as MSIR and MSC were not significantly different as shown in Table 4. Also given is the mean duration of MSC, 10 days, which certainly precludes invoking a placebo effect as rationale for patient analgesia.

The patient rating of pain intensity, pain relief and activity are shown in Table 5 for both MSIR q 4 h and MSC q 8 or 12 h. Identical descriptor scales were completed by the Nurse-Observer with results virtually identical to those reported by the patients. Regarding these three parameters, patients reported comparable results with MSC relative to MSIR. Of note, while acceptable analgesia was achieved for all patients, a number of patients found moderate pain relief to be acceptable while others desired and/or achieved a greater decrease in pain intensity. The Investigator's clinical judgment and experience is that acceptable analgesia is the goal of pain therapy since, often, total elimination of pain is impossible for cancer patients.

The acceptability of the MSC q 8 or 12 h regimens compared with the active control, MSIR q 4 h was quantified by the number of rescue analgesics required. Table 6 describes the use of rescue analgesics during a 48 hour period of acceptable dosing with MSIR and MSC. The test drug, MSC required only 6% more morphine sulfate (immediate-release) as rescue on a daily basis than was required for MSIR, a difference which is not statistically significant.

The Investigator's evaluation of MSC was made relative to both the active control (MSIR) and the historical control (previous or prestudy analgesic). The Investigator used the patient's diary and interviews to arrive at a global evaluation of the test drug. Pain relief,

convenience of dosing and quality of life were factors used in arriving at the evaluations presented in Table 7. Parts A and C of this table clearly show the preference for MSC regarding efficacy compared with MSIR and prior analgesic.

C. Safety Evaluations

As can be seen in Table 7B and D, the Investigator judged the side effects with MSC to be the same or fewer than noted when patients were on MSIR or their prestudy analgesic. Notable side effects which the Investigator judged should be reported as adverse reactions are displayed in Table 8. Two (2) of the five (5) patients involved were on MSC with only constipation directly linked to MSC. According to Table 5 (#3) some patients did feel sleepy while on both morphine preparations; however, apparently this condition was considered acceptable and no such adverse reaction was recorded. Overall no serious or unexpected untoward reactions were noted with MSC or with the active morphine control (MSIR).

D. Sensitivity of Experimental Procedure

A basic design requirement for analgesic studies is assay sensitivity. That is, it is necessary to assure that patients actually require a certain level of analgesic to achieve acceptable pain relief. If an analgesic regimen provides acceptable yet less than total pain relief, it is reasonable to assume the level of drug employed was, if fact, necessary to achieve the degree of analgesia reported. In addition, if rescue analgesics are required then the amount of test analgesic given must have been necessary to afford the degree of analgesia reported. This especially true in light of the patient's historical need for narcotics at a level substantially above the dose of rescue reported.

In this study the degree of pain relief while acceptable to all patients was not total for most patients (Table 5) either on the active control (MSIR) or test drug (MSC). However, while on MSC complete pain relief was achieved for 7% of patients whereas MSIR did not provide total relief of pain for any patients. Also, approximately 13 of 30 patients for both morphine preparations required rescue analgesics.

These considerations provide reasonable assurance that the experimental procedure could discriminate an active or test analgesic from placebo. This indirect but realistic measure of assay sensitivity circumvents the unacceptable technique of giving placebo in a chronic dosing pain study

lasting several days. This is especially so in this study where pateints required approximately 300 mg of morphine daily for pain control. Similarly, the chronic dosing design of this study in which test drug (MSC) was given over many days obviated the need for blinding since an analgesic placebo effect lasting greater than 24 hours is highly unlikely.

V SUMMARY AND CONCLUSIONS

Thirty (30) of thirty-eight (38) cancer patients completed this dosing-range study with no dropouts attributable to MS Contin. The study was designed to reflect a real clinical situation in which an analgesic is titrated to a level achieving adequate analgesia with acceptable side effects. Since the MS Contin 30 mg Tablet is equivalent to MST Continus 30 mg Tablet, the European experience with the British tablet should be paralleled by that of MS Contin. This hypothesis as confirmed with all completed patients achieving acceptable pain relief on a q 12 hour or q 8 hour dosing regimen with MS Contin 30 mg Tablet(s). Patients had previously been prescribed a narcotic analgesic and, overall, these encompassed many of the commonly used opioids. Regardless of the particular narcotic previously used, each completing patient was successfully converted to MS Contin q 12 or q 8 h. Of note, 100% of the patients who were placed on the q 12 h regimen with MSC realized acceptable pain control. Also, the amount of MSC required per 24 hours was not statistically different from that needed as MSIR, that is, approximately 300 mg.

The patients reported pain relief with MSC q 8-12 h to be slightly, although not significantly, better than with MSIR q 4 h whereas the Investigator evaluated MSC to be at least better for 53% of the patients relative to MSIR. Presumably the Investigator considered other "quality of life" advantages in addition to pain relief when evaluating MSC's efficacy relative to MSIR. In the judgment of the Investigator and relative to the patient's prestudy analgesic, MSC was at least better in all cases. Nearly 90% of the patients according to the Investigator experienced equal or fewer side effects compared to those noted on MSIR or the prestudy analgesic. Regarding notable untoward effects or adverse reactions, constipation was a repeated complaint, a reaction not unexpected with morphine therapy.

These findings based on a realistic therapeutic study design support the safety and efficacy of MS Contin 30 mg Tablet for the prolonged relief of severe pain when dosed q 12 h.

VI REFERENCES

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TABLE 1

DEMOGRAPHY

SEX: FEMALE	18	
MALE	12	
TOTAL	30	
RACE: WHITE	27	
BLACK	3	
MEAN HEIGHT (CM)	166.1	(N = 30)
MEAN WEIGHT (KG)	60.2	(N = 30)
MEAN AGE (YEARS)	49.4	(N = 30)

ONCOLOGIC DISEASE

NUMBER	LOCATION OR TYPE
3	Breast
6	Lung
5	Colon
7	Cervix
3	Prostate
1	Ovary
1	Osteogenic sarcoma
1	Testicle
1	Pancreas
1	Liver
1	Malignant Melanoma

TABLE 2

PATIENTS NOT COMPLETING STUDY

SEX:	FEMALE	2
	MALE	6
RACE:	WHITE	6
	BLACK	1
	HISPANIC	1
MEAN HEIGHT (CM)		167.4 (N = 8)
MEAN WEIGHT (KG)		61.0 (N = 8)
MEAN AGE (YEARS):		47.3 (N = 8)

	Phase of Study When Discontinued		
REASON FOR NOT COMPLETING:	MSIR	MSC	TOTAL
1) ILLNESS NOT DUE TO DRUG	3	1	4
2) ADVERSE REACTIONS*	4	0	4
TOTAL	7	1	8

*MSIR: 1) Abdominal pain, nausea, anorexia, constipation, diaphoresis, chills
2) Nausea/vomiting
3) Increase sleeping and confusion
4) Nausea/vomiting

TABLE 3

PRESTUDY ANALGESIC REGIMENS

Morphine 60 mg q 4 h
Morphine 25 mg q 4 h
Methadone 5 mg q 12 h plus Percocet 2 tabs q 3 h
Percocet 2 tabs q 3 h
Morphine 20 mg q 3 h
Morphine 5 mg q 1 h
Percocet 1.5 tabs prn
Levo-Dromoran 6 mg q 4 prn
Morphine 60 mg q 3.5 prn
Percocet 2 tabs prn
Dilaudid 8 mg q 2.5 prn plus Tylenol 2 tabs q 2.5 prn
Dilaudid 5 mg q 3.5 prn
Levo-Dromoran 3 mg q 4 plus Tylenol 2 tabs q 4
Percocet 2 tabs q 4 h
Levo-Dromoran 4 mg q 3 h
Percocet 2 tabs q 3 h
Percocet 3-4 tabs q 3.5 prn
Demerol 100 mg q 3 h
Morphine 25 mg q 3 h
Morphine 40 mg q 3
Demerol 50 mg q 4 prn
Levo-Dromoran 8 mg q 4 prn
Percocet 1 tab q 4 prn plus E. Strength Tylenol 1 tab q 4 prn
Dilaudid 6 mg q 3 prn
Methadone 20 mg q 4 prn
Levo-Dromoran 4 mg q 4 prn
Dilaudid 6 mg q 3.5 prn
Morphine 10 mg q 3 prn
Dilaudid 4 mg q 4 prn
Percocet 2 tabs q 3.5 prn plus Tylenol 2 tabs q 3.5 prn
Dilaudid 8 mg q 3 prn plus E. Strength Tylenol 2 tabs q 3 prn
Morphine 60 mg q 4 plus Tylenol 2 tabs q 4
Morphine 10 mg q 3.5 prn
Percocet 1 tab q 3 plus Tylenol 1 tab q 6 h
Dilaudid 20 mg q 3.5 prn
Dilaudid 36 mg q 4 prn plus Methadone 10 mg q 4 prn
Methadone 10 mg q 6 h
Morphine 4 mg sq/iv prn
Note: All doses are p.o. unless otherwise indicated.

TABLE 4

MORPHINE REGIMEN DATA

Frequency of MSC	N
q 8 h	16
q 12 h	14

Frequency of Success for Patients Tried on MSC at q 12 h

q 12 h	N	
successes	14	100%
attempted	14	
not-attempted*	16	

*(usual reason was patient was satisfied on q 8 h and refused frequency extension)

	Mean Total Daily Dose	S.E.	Mean # of Days on Drug
MSIR	298 mg	36.75	8.2
MSC	323 mg	42.66	10.6

$t_d = 1.17$ NS

TABLE 5

NUMBER OF PATIENTS REPORTING STATED CATEGORY AND PERCENTAGE OF CASES

1) Intensity of Pain

	None	Slight	Moderate	Severe	Total
MSIR	0	12	18	0	30
%	(0)	(40.0)	(60.0)	(0)	(100)
MSC	2	10	18	0	30
%	(6.7)	(33.3)	(60.0)	(0)	(100)

2) Relief of Pain

	None	Slight	Moderate	Lots	Complete	Total*
MSIR	0	3	13	12	0	28
%	(0)	(10.7)	(46.4)	(42.8)	(0)	(100)
MSC	0	1	16	9	2	28
%	(0)	(3.6)	(57.1)	(32.1)	(7.1)	(100)

*Note: Two patients could not make a firm decision in this category

3) Activity of Patient

	Awake Alert	Sleepy Often	Asleep Often	Total
MSIR	19	10	1	30
%	(63.3)	(33.3)	(3.3)	(100)
MSC	16	14	0	30
%	(53.3)	(46.7)	(0)	(100)

Note: No statistical difference was obtained between MSC and MSIR for each of the three parameters.

TABLE 6

RESCUE MEDICATION

48 HOUR PERIODS OF ACCEPTABLE ANALGESIA		
	STUDY DRUG	
	MSIR	MSC
NUMBER OF PATIENTS	12	13
NUMBER OF DOSES	29	33
MEAN 48 HOUR MORPHINE DOSE	53 mg	96 mg*
	SE=14.6	SE=24.4

*Difference is not significant p > 0.15

TABLE 7

INVESTIGATOR'S GLOBAL EVALUATION OF MS CONTIN COMPARED WITH MSIR AND PRESTUDY ANALGESIC*

Actual Response		Grouped Response	Observed	Expected*	Deviation	$(O-E)^2/E$
(A) EVALUATION OF EFFICACY RELATIVE TO MSIR						
MSC SUPERIOR	3/30	"Better"	16	10	6	3.6
MSC BETTER	13/30					
MSC SAME	12/30	"Equal"	12	10	2	0.4
MSC INFERIOR	0/18	"Inferior"	2	10	-8	6.4
$X^2_2 = 10.40$ P = 0.009						
(B) EVALUATION OF SIDE EFFECTS (SE) RELATIVE TO MSIR						
MSC NO SE	2/30	"Better"	12	10	2	0.4
MSC VERY FEW SE	6/30					
MSC FEW SE	4/30					
MSC SAME SE	14/30	"Equal"	14	10	4	1.6
MSC MORE SE	4/30	"Inferior"	4	10	-6	3.6
$X^2_2 = 5.60$ P = 0.07						
(C) EVALUATION OF EFFICACY OF MSC RELATIVE TO PRIOR ANALGESIC						
MSC SUPERIOR	9/30	"Better"	30	10	20	40
MSC BETTER	21/30					
MSC SAME	0/30	"Equal"	0	10	-10	10
MSC INFERIOR	0/30	"Inferior"	0	10	-10	10
$X^2_2 = 60.0$ P < 0.001						
(D) EVALUATION OF SIDE EFFECTS (SE) OF MSC RELATIVE TO PRIOR ANALGESIC						
MSC HAD NO SE	3/30	"Better"	19	10	9	8.1
MSC VERY FEW SE	8/30					
MSC FEW SE	8/30					
MSC SAME SE	8/30	"Equal"	8	10	-2	0.4
MSC MORE SE	3/30	"Inferior"	3	10	-7	4.9
$X^2_2 = 13.4$ P = 0.001						

*Note: Statistical comparisons were based on the assumption of random choice of "Better", "Equal" or "Inferior" as the hypothesis against which results were tested.

TABLE 8

ADVERSE REACTIONS

MS Contin	Adverse Reaction	Severity	Drug Induced
Pt. 23	Constipation	Moderate	Uncertain
Pt. 81	Depression	Moderate	Uncertain
	Constipation	Moderate	Yes
	Dizzy	Moderate	Uncertain
	Exhaustion	Moderate	Uncertain
	Nausea	Mild	Uncertain
Morphine Sulfate Immediate Release			
Pt. 5	Dizzy	Severe	Yes
Pt. 87	Nausea	Severe	Yes
	Vomiting	Severe	Yes
Pt. 90	Nausea	Severe	Yes
	Vomiting	Severe	Yes